Short-term exposure to carbon monoxide and myocardial infarction: A systematic review and meta-analysis

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Short-term exposure to carbon monoxide and myocardial infarction: *A systematic review and meta-analysis*

Kuan Ken Lee[a,1], Nicholas Spath[a,1], Mark R. Miller[a], Nicholas L. Mills[a,b], Anoop S.V. Shah[a,b,*]

[a] BHF Centre for Cardiovascular Science, University of Edinburgh, United Kingdom
[b] Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, United Kingdom

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ABSTRACT

Background: Previous studies suggest an association between short-term exposure to carbon monoxide and myocardial infarction. We performed a systematic review and meta-analysis to assess current evidence on this association to support the update of the World Health Organization (WHO) Global Air Quality Guidelines.

Methods: We searched Medline, Embase and Cochrane Central Register of Controlled Trials to update the evidence published in a previous systematic review up to 30th September 2018 for studies investigating the association between short-term exposure to ambient carbon monoxide (up to lag of seven days) and emergency department visits or hospital admissions and mortality due to myocardial infarction. Two reviewers assessed potentially eligible studies and performed data extraction independently. Random-effects meta-analysis was used to derive the pooled risk estimate per 1 mg/m^3 increase in ambient carbon monoxide concentration. Risk of bias in individual studies was assessed using a domain-based assessment tool. The overall certainty of the body of evidence was evaluated using an adapted certainty of evidence assessment framework.

Results: We evaluated 1,038 articles from the previous review and our updated literature search, of which, 26 satisfied our inclusion criteria. Overall, myocardial infarction was associated with exposure to ambient carbon monoxide concentration (risk ratio of 1.052, 95% confidence interval 1.017–1.089 per 1 mg/m^3 increase). A third of studies were assessed to be at high risk of bias (RoB) due to inadequate adjustment for confounding. Using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, the overall evidence was assessed to be of moderate certainty.

Conclusions: This review demonstrated that the pooled risk ratio for myocardial infarction was 1.052 (95% CI 1.017–1.089) per 1 mg/m^3 increase in ambient carbon monoxide concentration. However, very few studies originated from low- and middle-income countries.

1. Introduction

Air pollution is a major environmental hazard to human health and a leading cause of mortality and morbidity worldwide. The World Health Organization (WHO) has published several volumes of Global Air Quality Guidelines (AQGs) to provide guidance to the public, especially to policy and other decision makers, on the health risks of air pollution. To incorporate the latest scientific evidence into the guidelines, an update of the WHO AQGs is currently coordinated by the WHO Regional Office for Europe's European Centre for Environment and Health (ECEH) in Bonn (Germany). This systematic review and meta-analysis on the association between short-term exposure to carbon monoxide and ischaemic heart disease has been developed to support this update.

Carbon monoxide is a colourless and odourless gas that is emitted primarily from incomplete combustion of fossil fuels. The most well-recognised pathophysiological effect of carbon monoxide is tissue hypoxia, due to its ability to bind with haemoglobin to form carboxyhaemoglobin. Controlled exposure studies have demonstrated that carbon monoxide exacerbates myocardial ischaemia particularly in individuals with pre-existing coronary artery disease (Allred et al., 1989). Furthermore, studies in cell and animal models at moderate to high carbon monoxide concentrations have suggested other potential non-hypoxic mechanisms such as oxidative stress, inflammation and endothelial dysfunction (Thom et al., 1997, 1999; Lo Iacono et al., 2011).

A previous systematic review and meta-analysis has reported a

* Corresponding author at: BHF/University Centre for Cardiovascular Science, SU.305 Chancellor's Building, University of Edinburgh, Edinburgh EH16 4SB, United Kingdom.
E-mail address: Anoop.Shah@ed.ac.uk (A.S.V. Shah).
[1] Contributed equally.

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significant association between short-term exposure to carbon monoxide and risk of myocardial infarction (Mustafić et al., 2012). Since then, numerous new epidemiological studies have been published. We aim to update the previous review to incorporate these contemporary studies into the AQGs and to evaluate the overall certainty of the evidence of the effect estimate.

2. Methods

2.1. Search strategy and selection criteria

In this review, we updated a previous review by Mustafic et al which ended their search on 28th November 2011 (Mustafić et al., 2012). We searched Ovid MEDLINE, Ovid EMBASE and Cochrane Central Register of Controlled Trials from 31st October 2011 to 30th September 2018 using combinations of the following keywords: “air pollution”, “carbon monoxide”, “MI”, “heart attack”, “acute coronary syndrome” for studies that matched our prespecified PECOS (Population, Exposure, Comparator, Outcome, Study design) criteria (Appendix 1). The full search strategy is detailed in (Appendix 2). The protocol (World Health Organization, 2014) was registered with the International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD42017076081.

We evaluated studies from the previous review by Mustafić et al. (2012) and the updated literature search that reported associations between short-term exposure (in the order of hours up to 7 days) to ambient air carbon monoxide and hospital admissions or mortality due to myocardial infarction. We included studies in the adult general population (over the age of 18 years) without geographical restrictions. Studies that exclusively evaluated exposure to carbon monoxide in occupational or indoor settings were excluded. We included myocardial infarction as the only ischaemic heart disease outcome because it is not possible to accurately define the time of onset of other ischaemic heart disease outcomes such as angina which manifest over a period of months to years. Furthermore, apart from myocardial infarction, other conditions within the spectrum of ischaemic heart disease are routinely managed in outpatient settings rather than in the Emergency Department or necessitating hospital admissions. We included both time series and case-crossover studies published in peer-reviewed journals with no language restrictions. Systematic reviews of these studies were screened for any additional articles.

Two reviewers (KKL & NS) independently screened titles and abstracts identified from the systematic search using the prespecified eligibility criteria. The full-texts of potentially relevant articles were independently assessed by two reviewers (KKL & NS). Any disagreement on inclusion was resolved by discussion and, if no consensus was reached, a third reviewer was consulted (AS). Additional information from study authors (where necessary) to resolve questions about eligibility were obtained. Reasons for excluding articles at this stage were recorded.

Full text screening and subsequent reviewer’s agreement were recorded in a list of included studies for systematic review, that was circulated with the whole systematic review team and the WHO Guideline Development Group to identify any additional potentially relevant missing studies (published or in press). Where data from the same study population, with complete geographical and temporal overlap, was reported in multiple publications, only the largest and the most complete study was included to avoid double counting.

2.2. Data extraction

Data extraction was conducted in duplicate but independently by two authors (KKL & NS) using a standardised form which included a full description of the study design, geographical location, characteristics of the study population, details on air pollutant exposure (including unit of measurement, mean/median, 5-95th percentile and range of concentrations measured), details on co-exposures, details on outcome assessment (ICD codes used or physician diagnosis), details of confounders measured and confounders adjusted for, data to calculate the effect estimates and their confidence intervals most adjusted for confounders and conflicts of interest. All disagreements were resolved by discussion. We contacted authors for additional data or clarification where required.

2.3. Assessment of risk of bias

A new domain-based risk of bias (RoB) assessment instrument, developed by a working group of experts convened by WHO, was used to assess all studies included in the meta-analysis (World Health Organization, 2020).

The full details of the RoB assessment instrument, including the detailed assessment criteria used for each domain, has been published online by World Health Organization (2020). In brief, there are six domains in the instrument: confounding, selection bias, exposure assessment, outcome measurement, missing data and selective reporting. Reviewer RoB judgments (high, moderate, low) were reported for each RoB domain for all studies included in this review. Each domain contains several subdomains. To come to an overall judgement for a domain, the following procedure was applied: if any of the subdomains was rated as high risk of bias, the whole domain was rated as high risk of bias; if all the subdomains was rated as low risk of bias, the whole domain was rated as low risk of bias; when at least one subdomain was rated as moderate risk of bias and none of the other subdomains was at high risk of bias, the whole domain was rated as moderate risk of bias. To evaluate each risk of bias domain independently, subgroup analyses were considered for each domain where there is significant discordance in the risk of bias rating.

All studies were independently assessed using the RoB tool by two reviewers (KKL & NS). Any disagreement was resolved by discussion, and if no consensus was reached, a third reviewed (AS) was consulted. A WHO working group methodologist reviewed the RoB assessment of 10% of the included studies to ensure that the RoB assessment instrument was applied accurately.

2.4. Data synthesis

Relative risk was used as the effect measure for the association across all studies. Since the prevalence of ischaemic heart disease is low, we considered hazard ratios and odds ratio as equivalent to relative risk. We assumed a loglinear exposure-outcome relationship to calculate relative risk for a standardized increment of 1 mg/m^3 of carbon monoxide across all studies. Risk estimates were therefore standardised using the following formula:

$$RR_{[standardized]} = (RR_{[original]})^{Increment(1)/Increment(original)}$$

2.5. Statistical analysis

Random effects meta-analysis was performed to pool risk estimates across studies using the general inverse variance method. Where studies have reported multiple risk estimates for subgroups of the study population separately, estimates were combined using a random-effects meta-analysis. The shortest time lag between exposure and outcome presented in each study was used to calculate the pooled effect size. R (version 3.5.1) was used to produce forest plots and to undertake random-effects meta-analysis.

We constructed funnel plots to examine for publication bias and assessed for asymmetry using Egger’s regression test. Statistical heterogeneity of effect estimates between studies (also inconsistency of study results) was assessed using tau-squared and presented as 80% prediction interval around the meta-estimate. This is different to the

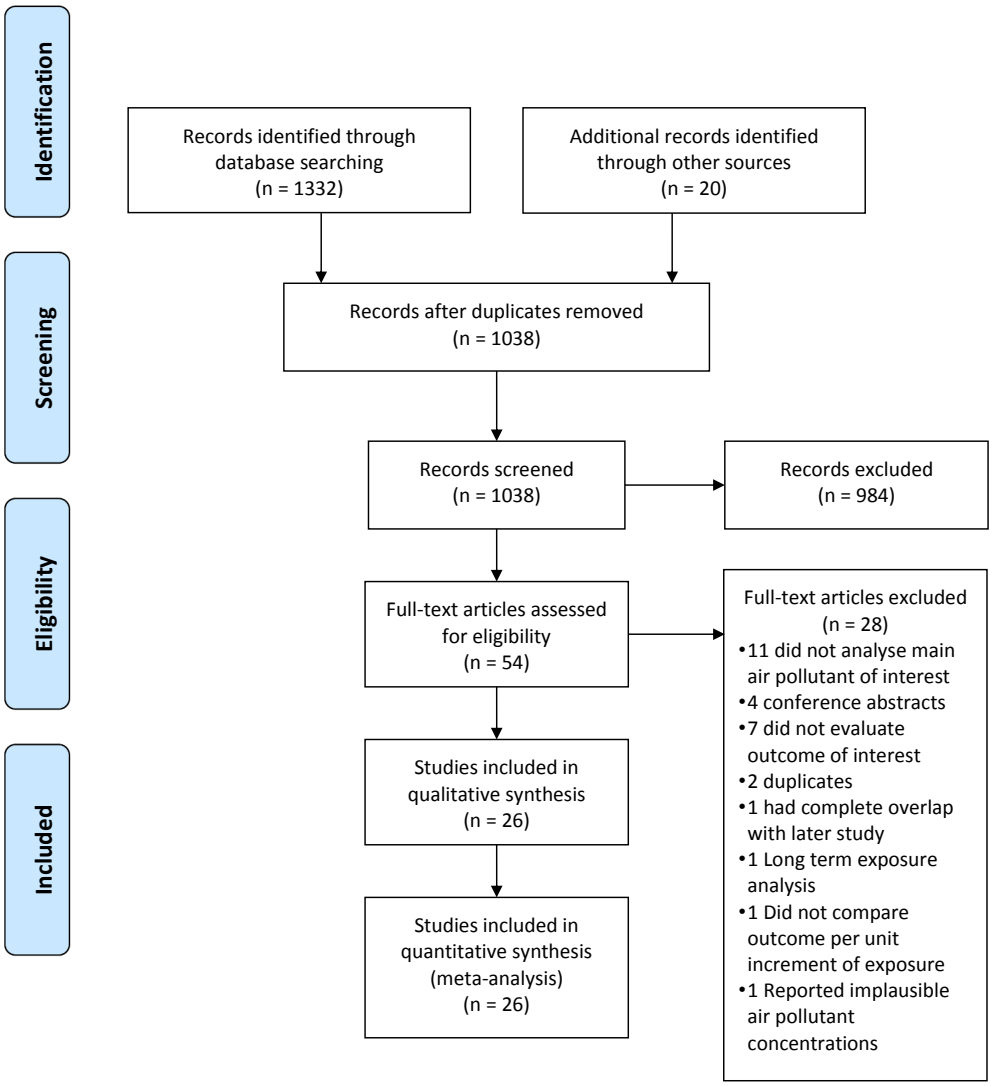

Fig. 1. Flowchart of assessment of eligible studies.

pre-specified protocol but following further deliberations by a WHO working group on certainty of evidence assessment, this was considered a more appropriate measure for statistical heterogeneity.

Where possible, we performed pre-specified analysis stratified by time lags, study design (time series versus case-crossover), age > 65 years versus ≤65 years, outcome: admission versus mortality, single versus co-pollutant modelling, studies with conflict of interest versus studies without conflicts of interest and stratified by risk of bias (high risk of bias versus low or moderate risk of bias within each domain where there was significant discordance across studies). We also performed further post-hoc subgroup analyses stratified by outcome definition, multi-city versus single-city studies, median year of publication and median pollutant concentration.

2.6. Evaluation of the certainty of evidence

The overall certainty of evidence was evaluated using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework that was conducted by a working group of experts convened by WHO (Morgan et al., 2019). Further information can be found in Appendix 3.

Due to the risk of unmeasured confounding in observational studies, the rating process started at moderate certainty. The quality of evidence was then downgraded or upgraded using prespecified criteria within domains of evaluation. Reasons for downgrading include limitations in studies, indirectness, inconsistency, imprecision and publication bias. Reasons for upgrading include large magnitude of effect size, all plausible confounding would shift relative risks towards the null and concentration–response gradient. The prespecified evaluation criteria used for each domain are briefly summarised below.

Limitations in studies: The certainty of evidence was downgraded if there were significant differences in the effect size in subgroup analyses stratified by high versus moderate or low risk of bias.

Indirectness: The certainty of evidence was downgraded if there were considerable differences between our prespecified PECOS of the systematic review and the PECOS used in the primary studies.

Inconsistency: This was evaluated by calculating the 80% prediction interval of the overall pooled meta-estimate (IntHout et al., 2016). If the 80% prediction interval was considerably wider than the confidence interval and overlapped with 1, this indicated considerable heterogeneity and the quality of the body of evidence was downgraded.

Imprecision: This was evaluated by calculating the sample size required to conduct an adequately powered study to detect the pooled risk estimate and confidence interval using the methodology developed by Rothman and Greenland (2018). If the total number of individuals across all studies included in the meta-analysis was considerably lower than the number that would be needed for an adequately powered study, the certainty of the evidence was downgraded because of

Table 1
Summary of characteristics of studies included in the systematic review.

Author and year	Study period	Study design	Mean CO concentration (mg/m^3)	Min-Max CO concentration (mg/m^3)	Outcome definition	Confounders measured	Effect Estimate (95% CI)*
Caussin et al. (2015)	2003–2008	Time-series	0.30	0–2.06	MI admission (physician diagnosis)	Long-term trends, Temperature, Day of Week	1.00 (0.90–1.10)
Wang et al. (2015)	1999–2010	Case-crossover	0.50	0–2.67	MI admission (ICD codes: I21-22 or 410)	Temperature, Humidity	0.98 (0.93–1.03)
Wang et al. (2015)	1999–2009	Case-crossover	0.35	0.12–0.81	MI admission (ICD codes: I21-22 or 410)	Temperature, Humidity	1.00 (1.01–1.00)
Milojevic et al. (2014)	2003–2009	Case-crossover	NR	NR	MI admission and mortality (physician diagnosis)	Seasonality, Long-term trends, Temperature, Temperature (non-linear), Day of Week	0.98 (0.96–1.01)
Mann et al. (2002)	1988–1995	Time-series	2.55	0.37–14.6	MI admission (ICD code: 410)	Temperature, Temperature (non-linear), Day of Week	1.02 (1.01–1.03)
Eilstein et al. (2001)	1984–1989	Time-series	1.82	0–12.8	MI admission (physician diagnosis)	Temperature, Humidity, Inlfuenza, Day of week	1.04 (0.99–1.09)
Sharovsky et al. (2004)	1996–1998	Time-series	4.56	1.23–14.6	MI mortality (ICD code: I21)	Seasonality, Temperature, Humidity, Pressure, Temperature (non-linear), Influenza, Day of week, Holiday	1.01 (1.00–1.03)
Lanki et al. (2006)	1992–2000	Time-series	NR	NR	MI admission (ICD code: I21-22, 410)	Temperature, Humidity, Pressure, Temperature (non-linear), Day of week, Holiday	1.03 (1.00–1.05)
Poloniecki et al. (1997)	1987–1994	Time-series	NR	0.25–12.3	MI admission (ICD code: 410)	Long-term trends, Temperature, Humidity, Day of week, Holiday	1.02 (1.01–1.03)
Linn et al. (2000)	1992–1995	Time-series	1.85	0.37–6.54	MI admission (physician diagnosis)	Seasonality, Temperature, Pressure, Temperature (non-linear), Day of week, Holiday	1.03 (1.02–1.05)
Peters et al. (2006)	1999–2001	Case-crossover	0.51	0.10–2.17	MI admission (physician diagnosis)	Long-term trends, Temperature, Pressure, Day of week	0.97 (0.71–1.32)
Sullivan et al. (2005)	1988–1994	Case-crossover	0.49	0.49–13.2	MI admission (physician diagnosis)	Temperature, Humidity, Day of week	1.03 (0.99–1.06)
Tsai et al. (2012)	1999–2009	Case-crossover	1.15	0.15–4.91	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Day of week	1.28 (1.20–1.37)
Liu et al. (2017)	2014–2015	Case-crossover	1.28	0.14–8.41	MI admission (ICD code: I21-22)	Seasonality, Long-term trends, Temperature, Humidity, Day of week	1.01 (1.00–1.02)
Lin et al. (2013)	1998–2010	Case-crossover	0.70	0.30–1.60	MI mortality (ICD codes: I21, 410)	Seasonality, Long-term trends, Temperature, Humidity, Day of week, Holidays	1.05 (0.98–1.13)
Bard et al. (2014)	2000–2007	Case-crossover	0.60	0.50–1.80	MI admission and mortality (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Influenza, Day of week, Holiday	1.37 (0.53–3.49)
Cendon et al. (2006)	1998–1999	Time-series	2.93	NR	MI admission (ICD code: I21)	Seasonality, Long-term trends, Temperature, Humidity	1.00 (0.93–1.07)
Berglind et al. (2010)	1993–1994	Case-crossover	0.51	NR	MI admission (physician diagnosis)	Seasonality, Long-term trends, Temperature, Humidity Temperature (non-linear), Day of week,	0.88 (0.49–1.57)
Barnett et al. (2006)	1998–2001	Case-crossover	NR	NR	MI admission (ICD code: I21-22, 410)	Seasonality, Long-term trends, Temperature, Humidity, Day of week, Holiday	1.02 (1.01–1.04)
Cheng et al. (2009)	1996–2006	Case-crossover	0.90	0.15–2.54	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Day of week	1.73 (1.46–2.04)
D'Ippoliti et al. (2003)	1995–1997	Case-crossover	3.7	NR	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Pressure, Temperature (non-linear), Day of week	1.02 (0.99–1.05)
Hsieh et al. (2010)	1996–2006	Case-crossover	1.46	0.15–4.91	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Pressure, Day of week	1.25 (1.18–1.32)
Nuvolone et al,(2011)	2002–2005	Case-crossover	1.03	NR	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Influenza, Day of week, Holidays	1.04 (0.98–1.09)

(*continued on next page*)

Table 1 (*continued*)

Author and year	Study period	Study design	Mean CO concentration (mg/m^3)	Min-Max CO concentration (mg/m^3)	Outcome definition	Confounders measured	Effect Estimate (95% CI)*
Peters et al. (2001)	1995–1996	Case-crossover	1.34	NR	MI admission (physician diagnosis)	Seasonality, Long-term trends, Temperature, Humidity, Temperature (non-linear), Day of week	1.09 (0.95–1.26)
Zanobetti and Schwartz (2006)	1995–1999	Case-crossover	NR	NR	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Humidity, Pressure, Temperature (non-linear), Day of week	1.10 (1.00–1.19)
Roye et al. (2018)	2001–2015	Time series	0.4	0–2.9	MI admission (ICD code: 410)	Seasonality, Long-term trends, Temperature, Influenza and Day of week.	1.00 (0.87, 1.15)

Abbreviations: CO = carbon monoxide; MI = myocardial infarction; NR = not reported.
* Effect estimates for the shortest lag per 1 mg/m^3 increment of carbon monoxide.

imprecision.

Publication bias: The certainty of evidence was downgraded if publication bias was detected by visual inspection of the funnel plot and confirmed using the Egger's test.

Large effect size: Magnitude of the effect size was assessed by calculating the E-value using the following formula:

$$E\text{-}value = RR + sqrt(RR*[RR-1])$$

The E-value quantifies the minimum strength of association on the risk ratio scale that an unmeasured confounder must have to negate the observed exposure-outcome association VanderWeele and Ding (2017) Therefore the certainty of evidence was upgraded if the E-value was substantially larger than the anticipated effect of a significant unmeasured confounder.

Confounding: The certainty of evidence was upgraded if the pooled risk estimate was positive despite the presence of other plausible confounding factors that would shift the risk estimates towards a null association.

Concentration–response gradient: The certainty of evidence was upgraded if a concentration–response association was observed, either linearly or non-linearly.

3. Results

Our updated literature search across MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials identified 1,332 articles. A further twenty articles that were included in the previous systematic review by Mustafic et al were also evaluated (Mustafić et al., 2012). The study selection process is detailed in Fig. 1. Following removal of duplicates, we assessed the titles and abstracts of 1,038 articles and reviewed 54 full text articles in depth. Of these, 26 articles fulfilled the inclusion criteria. This consists of 17 articles from the previous review and 9 from the updated literature search. Three studies from the previous review were excluded due to complete geographical and temporal overlap with a subsequent study (Bhaskaran et al., 2011) and inconsistency with our outcome of interest (Hoek et al., 2000; Stieb et al., 2009).

A detailed description of the 26 studies included are presented in Table 1. These studies originated from 14 different countries and were mainly conducted from the 1980s and 1990s. Mean concentration of carbon monoxide measured in these studies ranged from 0.3 mg/m^3 to 4.6 mg/m^3. Seventeen studies used a time series design and nine studies used a case crossover design. Most studies identified events from administrative databases using ICD-9 and ICD-10 codes. The majority of studies presented risk estimates for hospitalisation due to myocardial infarction (24 studies, 86%) whilst only 3 studies have reported risk estimates for mortality due to myocardial infarction.

3.1. Overall analysis

The pooled relative risk across all included studies was 1.052 (95% confidence interval [CI] 1.017 to 1.089) per 1 mg/m^3 increase in carbon monoxide concentration (Fig. 2). We observed significant heterogeneity for the overall pooled estimate (Tau^2 = 0.006). The funnel plot did not demonstrate any significant asymmetry (Fig. 3).

3.2. Risk of bias assessment

All 26 studies included in this review were evaluated using the RoB instrument across 6 domains (Appendix 4). We summarized adjustment for important confounders in the individual studies (seasonality, long-term trends, temperature, day of week, humidity, pressure, influenza, and holidays) in Table 1. There was significant variation in the adjustment for potential confounders across studies. All studies used appropriate analysis methods or study design to control for confounders. However, nine studies were assessed to be at high RoB for this domain.

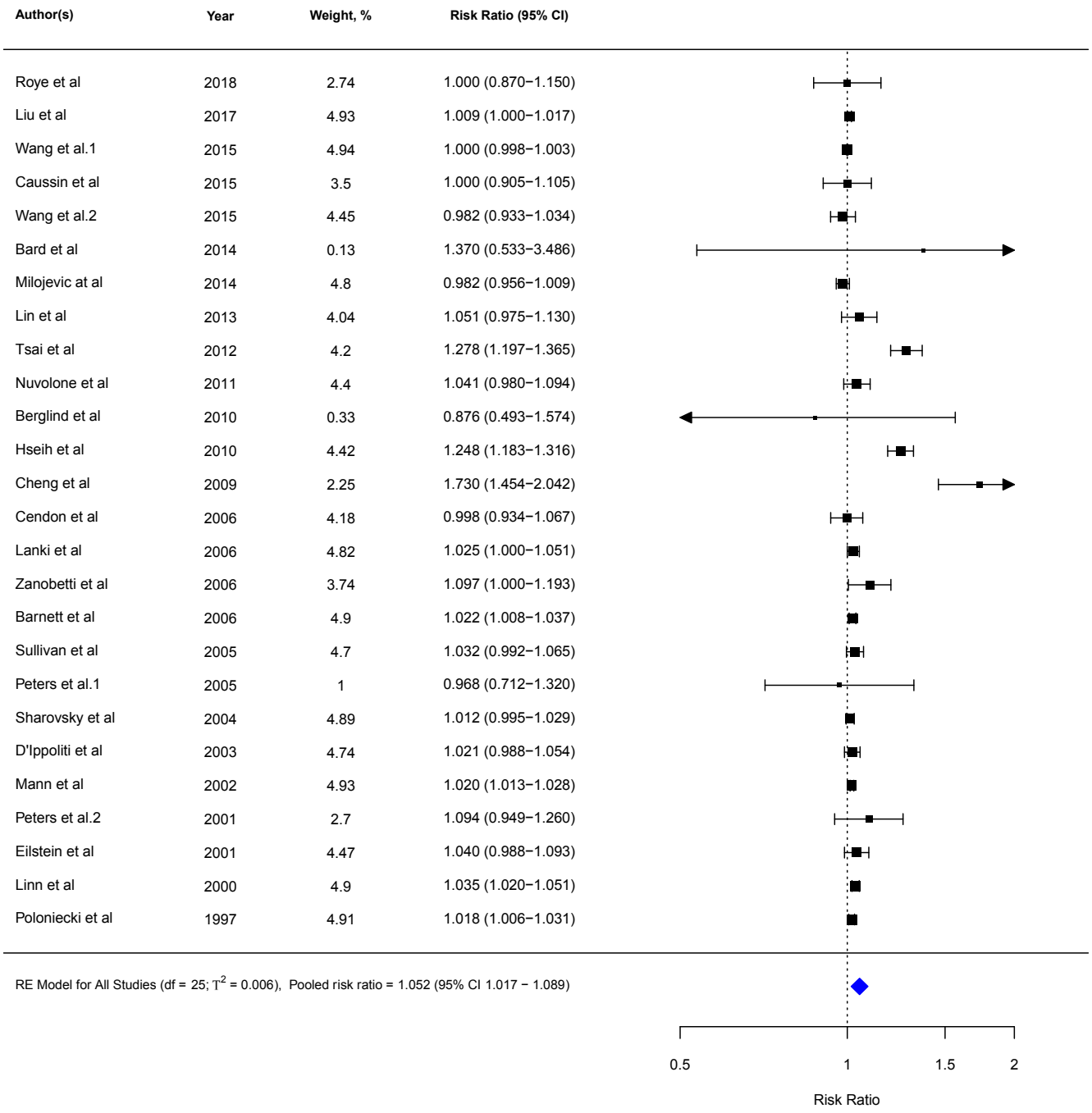

Fig. 2. Forest plot of the association between carbon monoxide and admission for MI or mortality from MI across all included studies.

Eight of these studies did not adjust for critical confounders such as seasonality, long-term trends or day of the week and one study (Peters et al., 2001) measured meteorological confounders from a single monitoring station but extrapolated the measurements across a large region. A further fifteen studies were assessed to be at moderate RoB for this domain because holidays or influenza epidemics were not adjusted in the analysis or the validity for measuring the meteorological confounders were insufficiently reported. Only two studies were at low RoB for confounder adjustment (Bard et al., 2014; Eilstein et al., 2001).

The majority of studies selected individuals from large administrative or healthcare databases without selection bias. However, three studies were assessed to be at high risk for selection bias. Two of these studies only included a highly-selected group of patients who were well enough to be interviewed (Peters et al., 2001; Berglind et al., 2010) whilst another study (Nuvolone et al., 2011) excluded a significant proportion of patients (14% of the total number of eligible patients) who have experienced previous myocardial infarction. Two other studies were assessed to be at moderate risk of selection bias. Lanki et al. (2006) only included patients below the age of 75 or 80 years whilst Mann et al. (2002) included only residents who were members of a regional healthcare insurance provider. These studies may have therefore introduced bias by selecting patients who have lower severity of ischaemic heart disease, fewer comorbidities or those who have a higher socioeconomic status.

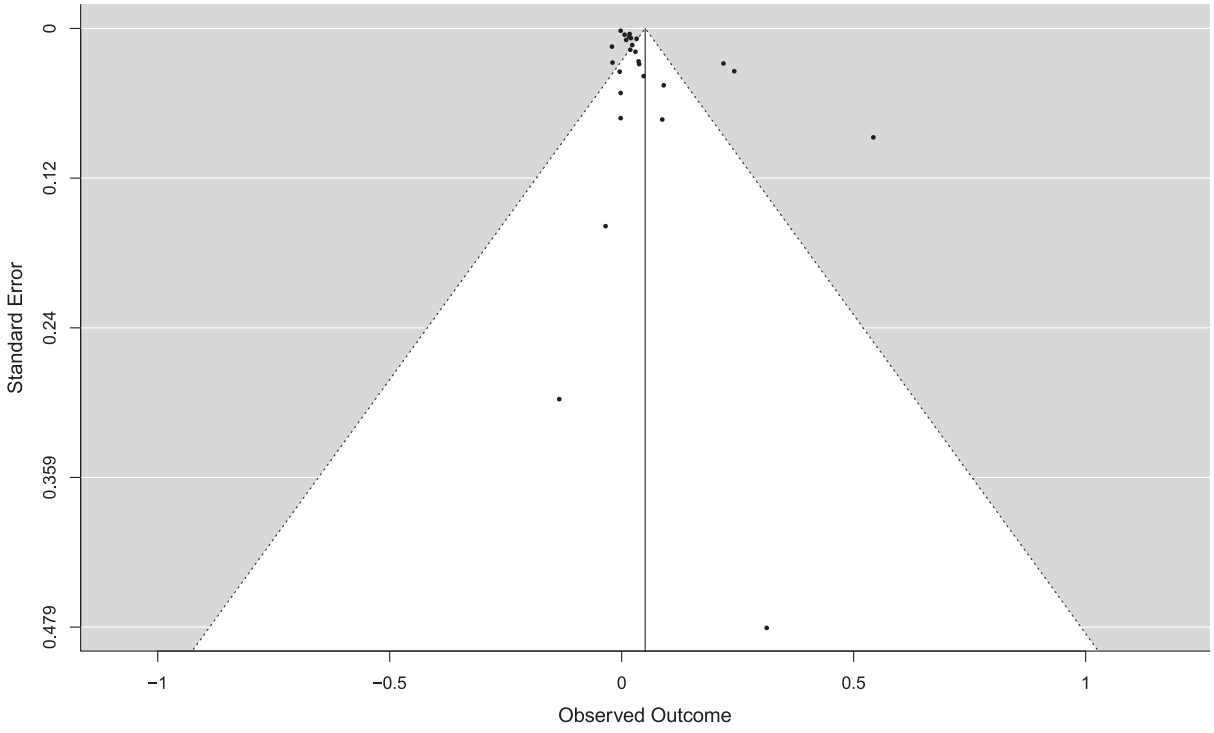

Fig. 3. Funnel plot.

All studies have measured exposure using daily averaged pollutant concentration obtained from air quality monitoring stations based within the cities. Two studies extrapolated pollutant measurements from a single air quality monitoring station across a large city and was therefore assessed to be at high risk of bias for exposure assessment (Peters et al., 2001; Zanobetti and Schwartz, 2006).

All studies used hospital databases or regional health registries to identify outcomes. These databases were linked with separate databases containing air pollutant and meteorological measurements. All outcome assessments were therefore blinded to the exposure measurement due to the study design. Most studies used ICD-9 or ICD-10 codes (18 studies) and the remaining 8 studies used physician diagnoses to define outcomes. All studies were therefore assessed to be at low risk of bias for this domain.

The majority of studies did not report the percentage of missing data but have utilised national or regional healthcare registries that were judged to have infrequent missing data and were therefore assessed to be at low risk of bias. Three studies were assessed to be at moderate risk of bias because missing exposure data was not infrequent but appropriate methods had possibly been used to account for it (Bard et al., 2014; Berglind et al., 2010; Lanki et al., 2006).

None of the studies had evidence of incomplete or selective reporting of effect estimates and therefore all were assessed to be at low risk of bias for this domain.

3.3. Subgroup analyses

Only 14 studies reported risk estimates stratified by individual lag days. Within this subset of studies, the association between carbon monoxide and myocardial infarction was present for up to three days before the event (lag 3, Fig. 4).

The association persisted when stratified by study design (Fig. 5). Association with mortality from myocardial infarction was 1.004 (95% CI 0.984 to 1.024), and 1.056 (95% CI 1.016 to 1.098) for hospitalisations due to myocardial infarction per 1 mg/m^3 increase in carbon monoxide concentration. Studies that defined myocardial infarction using ICD coding had a pooled relative risk of 1.068 (1.016 to 1.124) and those that utilised physician diagnosis had a pooled relative risk of 1.020 (0.997 to 1.044). Time series studies had pooled relative risk of 1.021 (95% CI 1.015 to 1.026) whilst case crossover studies had a pooled relative risk of 1.082 (95% CI 1.017 to 1.150) per 1 mg/m^3 increase in carbon monoxide concentration.

We performed subgroup analysis stratified by risk of bias due to adjustment for confounding. Studies that were at low or moderate RoB for this domain had a pooled relative risk of 1.082 (95% CI 1.020 to 1.148) per 1 mg/m^3 increase in carbon monoxide concentration but the association was attenuated in studies that were assessed to be at high RoB (pooled relative risk of 1.007 [95% CI 1.002 to 1.011]). Because very few studies were judged to be at high RoB in the other domains, no further subgroup analysis for RoB was performed.

We also performed subgroup analyses stratified by median year of publication and location of studies (1.022 [1.017–1.027] for studies published before 2007 versus 1.090 [1.002–1.186] for studies published from 2007 onwards and 1.012 [1.003–1.021] for multi-city studies versus 1.094 [1.014–1.180] for single-city studies. Studies with median carbon monoxide concentration below the median of 1.15 mg/m^3 had a pooled relative risk of 1.068 (95% CI 0.958 to 1.189) per 1 mg/m^3 increment whilst studies with median carbon monoxide concentration above 1.15 mg/m^3 had a pooled relative risk of 1.044 (95% CI 1.006 to 1.082).

Meta-regression analysis across did not identify any statistically significant heterogeneity across subgroups. We were not able to perform subgroup analysis by sex, age, multipollutant studies or conflict of interest because there were too few studies reporting risk estimates stratified by these subgroups.

3.4. Sensitivity analysis

Three studies (Hsieh et al., 2010; Cheng et al., 2009; Tsai et al., 2012) performed by a single research group reported substantially higher risk estimates compared to other included studies. Of these, two had substantial temporal and geographical overlap (Hsieh et al., 2010; Tsai et al., 2012). A sensitivity analysis was therefore performed excluding these studies (Appendix 6). The overall meta-estimate was

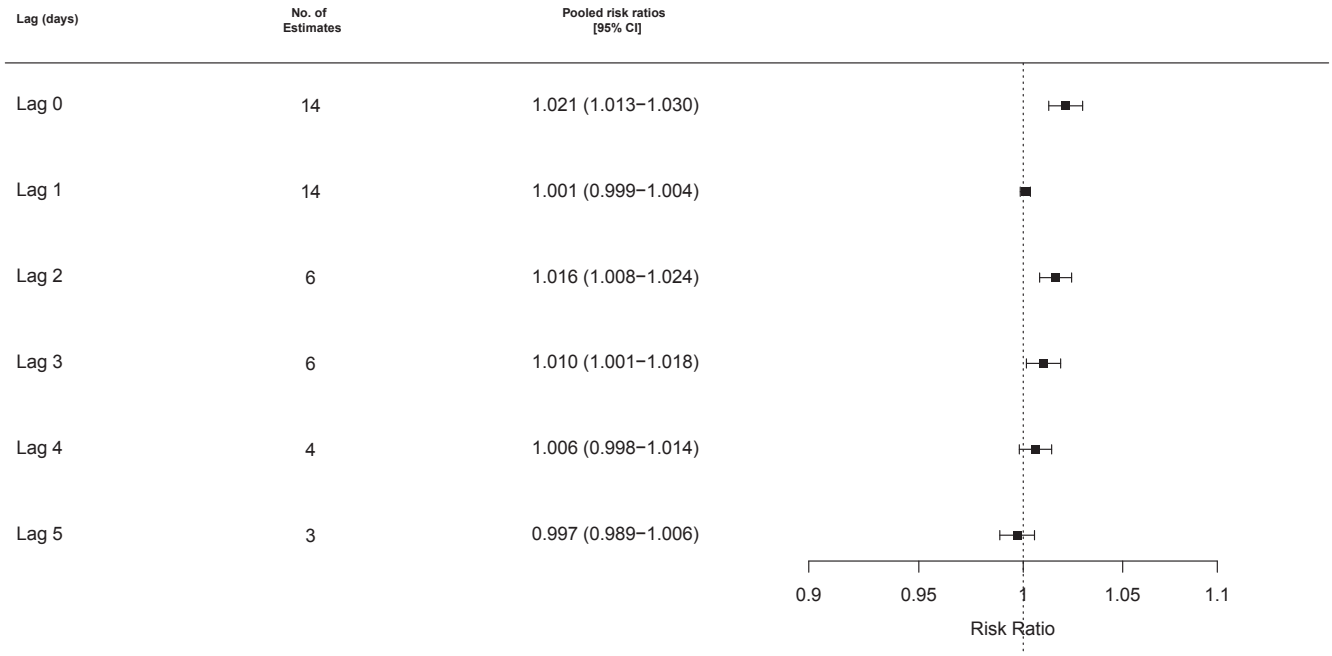

Fig. 4. Association between carbon monoxide and admission for MI or mortality from MI stratified by time lags.

attenuated (pooled relative risk of 1.016 [95% CI 1.009 to 1.023]). All three of these studies were assessed to be at moderate risk of bias. Subgroup analysis stratified by risk of bias demonstrated less heterogeneity (1.019 [1.009–1.029] in studies at low/moderate risk of bias versus 1.007 [1.002–1.011] for studies at high risk of bias; P-value for meta-regression = 0.365).

4. Discussion

In this systematic review and meta-analysis update, we have identified ten additional studies evaluating the short-term effects of carbon monoxide on admission to hospital for myocardial infarction or mortality from myocardial infarction. After incorporating the newly identified studies, our pooled estimate across 26 studies demonstrated that the pooled risk ratio for myocardial infarction was 1.052 (95% CI 1.017 to 1.089; 80% prediction interval 0.95–1.16) per 1 mg/m^3 increase in ambient carbon monoxide concentration. The magnitude of the association was very similar with the previous meta-analysis of 20 studies by Mustafić et al. (2012).

We identified 3 studies that reported substantially higher risk estimates than other included studies (Hsieh et al., 2010; Cheng et al., 2009; Tsai et al., 2012). These 3 studies were performed by the same research group. Importantly, the ambient carbon monoxide concentrations in the cities at which the studies were conducted were

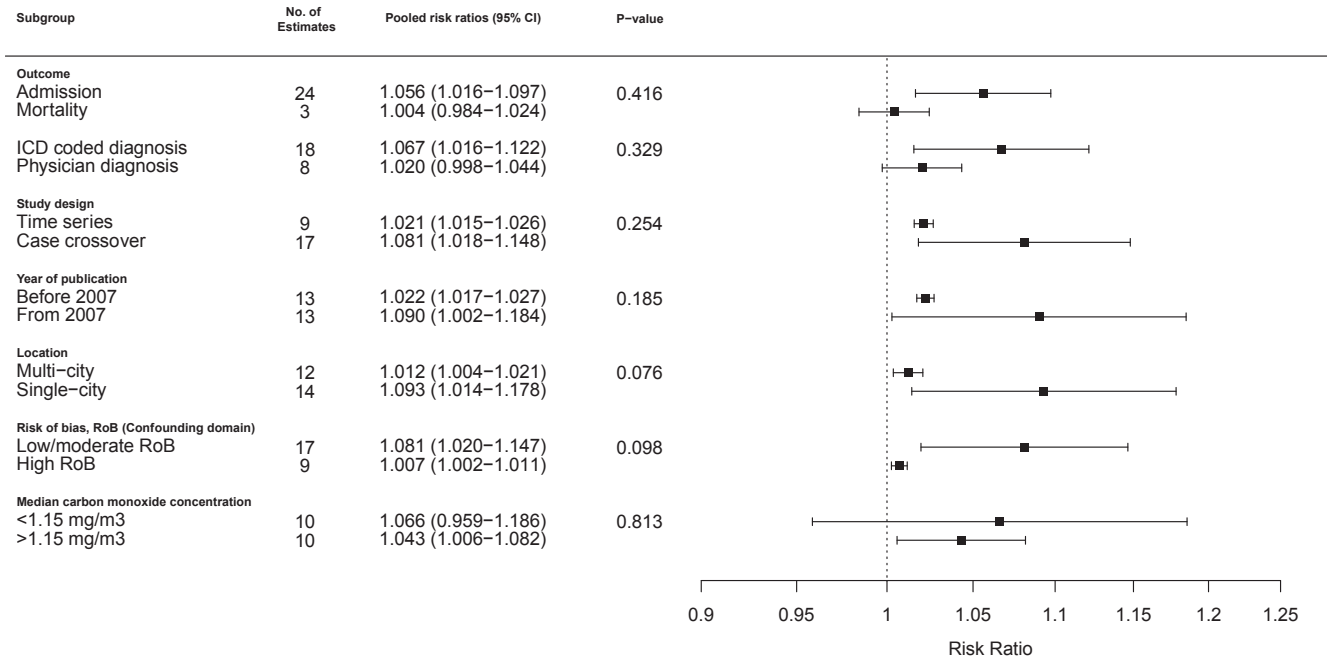

Fig. 5. Association between carbon monoxide and admission for MI or mortality from MI stratified by subgroups. Abbreviations: ICD = international classification of disease; RoB = risk of bias.

relatively low, conversely, ambient nitrogen dioxide and PM_{10} concentrations were relatively high. Two-pollutant analyses performed in these studies indicate that carbon monoxide may have been substantially correlated with other pollutants, therefore potentially confounding the risk estimates for carbon monoxide. Sensitivity analysis excluding these studies attenuated the overall pooled risk estimates and reduced the amount of heterogeneity across subgroups.

We evaluated the overall certainty of the evidence using the adapted certainty of evidence assessment framework agreed by the Guideline Development Group. First, a third of the studies had high risk of bias due to inadequate adjustment for confounding. Subgroup analysis showed that the risk estimate was lower in studies at high risk of bias compared to those at low or moderate risk of bias although this was not statistically significant. In sensitivity analyses excluding 3 outlying studies, the subgroup risk estimates were similar. For this reason, we have not downgraded the overall certainty of the evidence due to limitations in the included studies. Second, studies included in the review were consistent with the PECOS stated in our pre-specified eligibility criteria; therefore, we did not downgrade due to indirectness. Third, the 80% prediction interval of the pooled risk estimate ranged from 0.871 to 1.271. However, most of the heterogeneity could be explained by the 3 studies that reported outlying results. Sensitivity analysis excluding these studies had an 80% prediction interval of 1.002–1.030. Therefore, the quality of the body of evidence was not downgraded due to inconsistency. Fourth, the number of individuals evaluated across the 30 studies included in this review was over 1.5 million. Although this is lower than the estimated sample size of 12.1 million required to assess the risk estimate using the calculation proposed by Rothman and Greenland (2018) the included studies reported risk estimates with sufficient precision. Furthermore, the calculation involved a number of assumptions on the risk in the general population, the proportion of the general population exposed to air pollution and homogeneity of risk across diverse geographical regions. Therefore, we have not downgraded the certainty of the evidence due to imprecision of the pooled effect size. Finally, visual inspection of the funnel plot does not indicate significant asymmetry therefore we have not downgraded the evidence due to publication bias.

The overall risk estimate of 1.052 is modest. An E-value of 1.29 was derived, however we have insufficient information to determine the strength of association between an unmeasured confounder and our outcome therefore we have not upgraded the certainty due to a large effect size. We also did not upgrade the certainty of evidence due to other plausible confounders as the direction of effect is unknown. Furthermore, none of the studies have reported evidence of a dose–response relationship between exposure to carbon monoxide and myocardial infarction.

In summary, the overall quality of the evidence on the association between short-term exposure to carbon monoxide and myocardial infarction was assessed to be of moderate certainty.

We acknowledge several limitations in this review. First, the vast majority of studies originated from high-income countries with only five out of thirty studies conducted in low- or middle-income countries. This may limit the generalisability of our findings. Second, the pooling of evidence from only observational studies is prone to bias. However, this is an issue that is common to environmental epidemiological studies in this field where it is not possible to conduct a randomised controlled trial. Finally, very few studies have performed multi-pollutant analyses. Ambient carbon monoxide concentrations may be highly correlated with other air pollutants such as nitrogen dioxide which may significantly confound the observed risk estimates.

5. Conclusions

In conclusion, the pooled relative risk across for myocardial infarction was 1.052 (95% CI 1.017–1.089; 80% prediction interval 0.871–1.271) per 1 mg/m^3 increase in ambient carbon monoxide concentration. Overall, the evidence was assessed to be of moderate quality. Further research in low- and middle-income countries is needed to improve the generalisability of our findings.

CRediT authorship contribution statement

Kuan Ken Lee: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing - original draft, Writing - review & editing. **Nicholas Spath:** Data curation, Investigation, Software, Writing - review & editing. **Mark R. Miller:** Writing - review & editing. **Nicholas L. Mills:** Writing - review & editing. **Anoop S.V. Shah:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105901.

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